REMARKS

Claims 1 to 33, 35, 38 to 40, and 71 to 97, 112 to 132 and 134-136 are pending in the application. Claims 135-136 have been added. Claims 1, 11, 14, 16, 25 and 73 have been amended. Support for amendments can be found throughout the specification, i.e., in claims as originally filed; in the working examples, or on pages 28, lines 4-18, page 34, lines 29-35 and page 35, lines 28-37 of the specification. No new matter is believed added.

Rejection of Claims under 35 USC §112

I. Rejection of Claims 1-33, 35, 38-40, 71-97 and 112-134 under 35 USC §112, first paragraph

Claims 1-33, 35, 38-40, 71-97 and 112-134 are rejected under 35 USC §112, first paragraph, as failing to comply with the written description requirement. Applicants respectfully traverse this rejection.

The Examiner has rejected the claims listed above with respect to the limitation "wherein the extruded capsule shell composition is substantially independent". (See Office Action, page 2, 3rd ¶, last line).

Applicants respectfully point out that support for the aforementioned limitation can be found on Page 24, lines 33-36 and page 25 lines 1-2:

> "One aspect of the present invention is the novel blending of components which has the ability to render the poly(meth)acrylates, such as 4135F, which are pH dependent independent of this characteristic. ***They are no longer governed by the pH of the solution, i.e. the gastric tract, but are time/controlled release dependent instead,*** which determination is based upon the addition of the swellable solids and surfactants which will be described in further detail herein."[emphasis added].

The above paragraph clearly states that the polymer blend is no longer pH dependent, e.g. it is pH independent, and controlled by the time it takes to have excipients in the formulation, such as the above noted 'swellable solids' hydrate accordingly.

Therefore, Applicants have met the written description requirement accordingly with respect to inclusion of this term in the claims.

The Examiner further comments that:

> "Contrary to the limitation in the claims, the examples from the present specification show that the release of active agent from the capsule is indeed pH-dependent. See for example pages 45 and 48 for the dissolution rate at pH greater than 6 or 7.5. (See Office Action, page 2, 3rd ¶, last line, one page 3, 1rst ¶, first line).

Applicants respectfully maintain that the present specification indicates that release of active agent from a capsule of the present invention is pH independent for the reasons discussed below.

The specification teaches it is possible to have differing release rates of the contents of the capsule shell, and differing rates of release of the linker from the capsule subunits. These differing release rates are determined by polymeric composition that the capsule shells and subunits are composed of. The primary polymer along with the amounts of and types of excipients added to the polymer determine whether the release will be immediate or delayed. These releases are categorized in the specification on page 34 as "Fast Release/Pulse Capsules or Components", and on page 35 as "Slow/delayed Release/Pulse Capsules or Components".

Taking excerpts from the specification on page 34, lines 25-35, the "Fast Release/Pulse Capsules or Components" can be manipulated for production of an early release/pulse capsule or component in a multidosage capsule to have a 2-4 hour window. This is achieved by blending the Eudragit 4135F with the appropriate excipients, and extruding and injection molding the composition into thin walled component shells. In one preferred embodiment of the invention, the experimental section demonstrates that a formulation comprising the polymer 4135F with a surfactant and a swellable solid produces stable, injection molded components which can be reliably reproduced and injected from the mold with reduced, or no warpage of the shell.

In another embodiment of the invention, components made by blending 4135F with a swellable solid (hydroxypropylcellulose), at various percentages ranging from 10 to 70% were tested for their variance in a dissolution times, in an appropriate dissolution apparatus. Formulations containing 40 to 70 % Klucel were found to have similar dissolutions times (<2hours) in both simulated gastric fluid (SGF) and simulated intestinal fluids (SIF).

Dissolutions times for formulations containing 10 to 30% Klucel were found to be longer and more variable, although it is clear that this resulted in moldable components.

With respect to the "Slow/delayed Release/Pulse Capsules or Components", the specification on page 35, lines 1-14 teaches that:

> "the principal problem with Eudragit® 4135F in its unformulated state is its high dissolution time, in ***excess of 30 hours in aqueous media*** e.g. in SIF (simulated intestinal fluid). Therefore, to improve its dissolution time the polymer is blended with one or more hydrophilic excipients. This will enhance the absorption of water by the Eudragit 4135F polymer, and so accelerate the rate at which the blended polymer swells on absorption of water. As noted by the Experimental section herein, a ***dissolution modifying excipient, preferably a swellable solid excipient*** and optionally a second dissolution modifying excipient, such as a disintegrant, a lubricating agent, and if desired a surfactant, will produce a stable, injection molded component which can be reliably reproduced and injected from the mold with reduced, or no warpage of the shell." [emphasis added]

As noted, unformulated Eudragit® 4135F has a very high dissolution time, in excess of 30 hours in aqueous media e.g. in SIF (simulated intestinal fluid). SIF is the testing fluid used in the various USP apparatus's and is referenced in the specification on page 45 by the Examiner. SIF has a pH of about 7.5. SIF mimics the intestinal fluids.

The development of 4135F with the swellable solid hydroxypropylcellulose was intended to deliver pulsatile units with earlier release times than the combination of 4135F with the swellable solid HPMC in combination with lactose or the 4135F polymer combination with a super-disintegrant. Dissolution profiles which show that this was achieved with the inclusion of hydroxypropylcellulose (Klucel LF) is shown below in Figure 1. This data is referenced in the specification and cited above as "Formulations containing 40 to 70 % Klucel were found to have similar dissolutions times (<2hours) in both simulated gastric fluid (SGF) and simulated intestinal fluids (SIF)."

The profile in this Figure demonstrates that shells composed of a combination of 4135F and Klucel LF had a much reduced dissolution time, (over unformulated 4135F) which is *unaffected by media pH.*

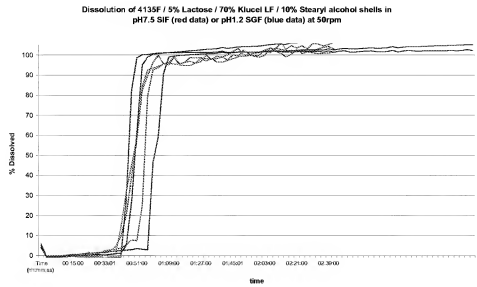


Figure 1: USP2 dissolution profile of 4135F/Klucel LF shells in SIF and SGF

This can be determined by looking at the blue lines which shows the dissolution of shells in pH 1.2 (e.g. Simulated Gastric Fluid) and those in the red lines which shows the dissolution of shells at pH 7.5 (e.g. Simulated Intestinal Fluid). As can be seen the red and blue lines overlap and appear quite similar. Thus, dissolution of these polymeric compositions is independent of the pH of the system in which they are tested in.

This clearly demonstrates that it is not only possible to manufacture shells with pulsatile release profiles, but that the release profiles are independent of buffer pH. The unmodified 4135F polymer therefore requires formulation modifications to achieve dissolution profiles which are comparable to other conventional enteric dosage forms.

Thus it is believed that Applicants have fully met the written description requirement, and that the specification fully supports this. Withdrawal of the rejection of these claims under 35 USC §112, first paragraph, is respectfully requested.

II. Rejection of Claim 25 under 35 USC §112, second paragraph

The Examiner has rejected claim 25 for the recitation of the phrase" at least one dissolution modifying excipient" in line 3. The Examiner points out that Claim 1 does not recite this

limitation, but instead requires "at least two dissolution modifying excipients" in the use of the phrase "combination".

Claim 25 has been amended to recite:

> "The capsule shell composition according to Claim 1 wherein the copolymer is present in an amount of about 50 to 90% w/w, the lubricant is stearyl alcohol present in an amount of about 10 to about 15% w/w, and the combination of dissolution modifying excipients contains at least one dissolution modifying excipient which is hydroxypropylmethylcellulose, hydroxypropylcellulose, or a hydroxylalkyl cellulose derivative or salt thereof. "

In view of this amendment and remarks, withdrawal of the rejection to claim 25 under 35 USC §112, second paragraph is respectfully requested.

Applicants have also amended claim 1 and 73 to recite "and a ratio of free carboxyl groups to esters groups of 1:10" with respect to the copolymer as in:

> "a copolymer of methyl acrylate, methyl methacrylate and methacrylic acid with a molar ratio of monomer units represented as 7:3:1, and a ratio of free carboxyl groups to esters groups of 1:10, present in an amount of about 20 to 90% w/w;

which is specifically disclosed in the manufactures data/specification sheet for the Eudragit 4135F. Applicants attach the specification sheet for the Examiner's convenience.

Rejection of Claims under 35 USC §103

The claims herein have three rejections as noted below:

I. Claims 1, 2 7-16, 20-22, 39, 40, 73, 74, 81-84, 87-90, 92-95, 112 and 113 are rejected under 35 USC §103(a) as being unpatentable over Petereit (US Pub. No. 2002/0160042), in view of Lehman et al, US 5,705,189 ('189).

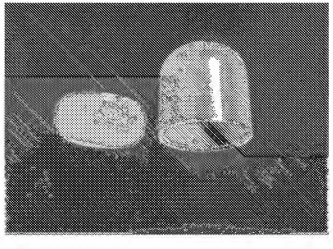
II. Rejection of Claims 3-6, 18 and 75-80 under 35 USC §103(a) over Petereit in view of Bolles (US 3,779,942) and Zentner (US 4,795,644).

III. Rejection of Claims 1-33, 35, 38-40, 71-97, 112-132 and 134 under 35 USC §103(a) over Petereit, in view of Lehmann I, Hatano (US 6,309,666) and Klug et al. (US 3,314809).

Applicants respectfully traverse all of these rejections. Although each of these rejections will be discussed independently below, the comments to Petereit is the primary reference will be referenced rather than repeated.

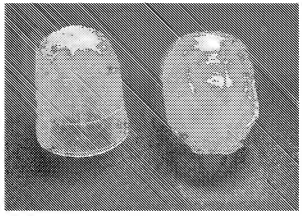
It should be noted that the Lehman Patent, US 5,705,189 ('189) has been referred to in earlier Office Actions and Responses as Lehman I, the details of which are incorporated by reference herein. The Petereit publication has also republished as US 2008/260814 (both of which correspond to previously cited WO 01/42935).

The present invention of independent claim 1 (capsule shells) and claim 73 (linkers) are directed to individual components of a multi-component dosage form. These components can include a capsule shell (of various sizes and shapes) and linker subunits, or end caps for shells, composed of these particular compositions. While representative pictures of capsules and sublinkers are disclosed in the Figures of the specification to assist the Examiner two of these pictures are produced below:



In the above Figure the linker subunit can easily be seen to have suitable ridges for the capsule component to be adhered or fixed to in a number of different ways.

In the Figure below an alternative capsule shape with ridges is demonstrated.



As noted in the specification the capsule shell and linker may be composed of the same or different compositions. Regardless of the composition of the subcomponents, they are meant to break apart at a particular time, and release the contents of the shell and/or linker to the GI tract at that time, all at once, not over a period of time as would be provided for in a controlled or constant rate of release. One dosage form that has a controlled, and constant rate of release of and active agent is the cited Zentner device, over which some of the claims are rejected herein.

The most frequently utilized capsule for drug delivery is a gelatin capsule. They are inexpensive, readily available, and provide what is termed 'immediate release'. When a gelatin capsule is administered, the capsule starts to immediately dissolve in the stomach and allows the contents of the capsule to be released into the gastrointestinal tract all at once (hence the term immediate release). In contrast, the 4135F polymeric blend of the instant invention instead provides for a capsule shell that has a more delayed, or prolonged time period before it releases the capsule contents into the GI tract. If a more immediate release of the capsule contents is desired, then a shell formulation which uses different polymers than the one claimed herein would be used. Such a capsule shell is described in copending application USSN 10/060,603 or USSN 10/470,439 which have claims directed to the polymer Eudragit E100, for instance.

Thus, when a multicomponent dosage form is assembled it is possible to have a shell subunit that disperses the contents as an immediate release, and be linked with a shell subunit that disperses the contents as a pulsitile release, much later down the GI tract. The same active or a different active can be filled into the capsule shells as desired.

A benefit of this invention is that the active agent need not be admixed with all the necessary excipients generally used for tableting. The greater the number of excipients the greater the chance for drug-excipient interactions which can affect stability of the active not just in shelf life, but with avoidance of potential degradants, etc. from these interactions.

The rejection under 35 USC §103(a) with respect to Petereit has been maintained, where the Examiner stats that Petereit:

> "…teaches injection-molded compositions comprising a) 45-100% methacrylate copolymers; b) 0.1-3% lubricant; c) 0-50% drier; d 0-30 plasticizer; e) 0-100% additives or auxiliaries; f) active agent; and g) 0-20% of another polymer of copolymer (paragraphs 0019-0027)." (See Office Action, page 3, 5th ¶); and
>
> Petereit "does not explicitly teach the claimed percent amount of lubricant from 5% to about 30%. However, difference in concentration will not support the patentability of subject matter encompassed by the prior art unless that is evidence indicating such concentration is critical…… In the present case, it would have been obvious to one of ordinary skill in the art to, by routine experimentation select a lubricant amount that falls within the claimed range with the expectation of at least similar result. This is because Petereit teaches the use of the same lubricant, such as stearyl alcohol, for the same purpose, namely, as a mold releasing agent (paragraphs 0041-0044). Further the use of lubricant as a mold releasing agent in the claimed amount is known in the art. See for example the teaching of Lehmann at column 3, lines 65-67; and example 1. Lehmann teaches the use of 6% of the mold releasing agent, based on the weight of the polymer. Accordingly, it would have been obvious to one of ordinary skill in the art to modify the molding compositions of Petereit using lubricant in the claimed amount in view of the teaching of Lehmann." (See Office Action, page 4, 2nd ¶).

Applicants respectfully traverse the above-identified rejection for these reasons.

Petereit et al. teaches an improvement in an injection molding process that includes a devolatilization step. The purpose of this devolatilization step is for removing residual traces of water from the copolymer which would interfere with the injection molding of the final product.

The formulation of the copolymer blend used in the Petereit process does not teach a combination of two (2) dissolution modifying agents as required by claim 1 herein. One of the dissolution modifying excipients for use in the instant invention is a swellable solid. In Petereit, there is no express statement of swellable solids, but use of a second copolymer. The copolymer is an optional excipient in Petereit's blend, being present from 0-20% w/w. Consequently, the resulting blend does NOT require such an excipient to being present.

The list of polymers suitable for use in the Petereit formulation in disclosed in paragraph 0080 shown below. This paragraph provides for a long list of many polymers not claimed or disclosed for use within the context of Applicants invention as a dissolution modifying excipient. Therefore, even if a copolymer is present one would not necessarily be directed to pick and choose as an excipient that one which Applicant describes as a dissolution modifying excipient.

Further, Paragraph 0080 does not provide for combinations or mixtures of these polymers as required by Applicants.

More importantly, and which has been raised previously, paragraph 0080 contains an error. As can be readily seen the recitation of hydroxypropylcellulose is followed by the abbreviation of HPMC as "hydroxypropylcellulose (HPMC)". However, HPMC stands for hydroxypropyl**methyl** cellulose NOT hydroxypropylcellulose. Therefore it is unclear if Petereit meant to include HPC or meant to include HPMC in the list of polymers disclosed therein.

> **[0080]** Examples of these other polymers are: polyvinylpyrrolidones, polyvinyl alcohols, cationic (meth)acrylate copolymers made from methyl methacrylate and/or ethyl acrylate and 2-dimethylaminoethyl methacrylate (EUDRAGIT® E100), carboxymethylcellulose salts, hydroxypropylcellulose (HPMC), neutral (meth)acrylate copolymers made from methyl methacrylate and ethyl acrylate (dry matter from EUDRAGIT® NE 30 D), copolymers made from methyl methacrylate and butyl methacrylate (PLASTOID® B) or (meth)acrylate copolymers with quaternary ammonium groups and containing trimethylammonioumethyl methacrylate chloride as monomer (EUDRAGIT® RL and/or EUDRAGIT® RS).

Consequently, all of the limitations of Applicant's Claim 1 are not present in the Petereit '042 publication.

The Lehman I '189 patent is directed to compositions which are pH dependent and dissolve in the intestinal juices, for use as controlled release coating agents. (see Abstract) In column 2, lines 31-36, Lehman states:

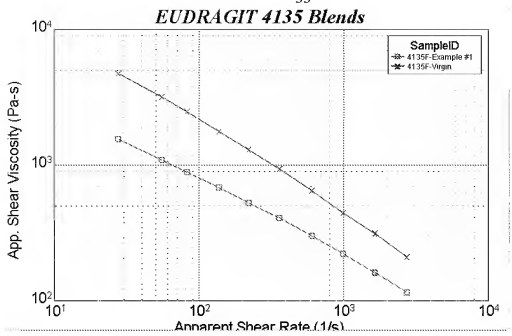
> "Drug coating produced therefrom,..... are not soluble in gastric juice at a pH 1 to 2 and in intestinal juices or buffer solutions with pH values $\leq$5, but can dissolve well in intestinal juices at pH values of 5.5 to 8."

This teaches formulations which are pH dependent, not pH independent. The presently amended claims, are however, directed to capsule shells and linkers molded from a composition which is **substantially pH independent.**

The Lehman I copolymer materials while primarily oriented towards drug coatings (Column 1, lines 61 to 67; and Column 2, lines 1 to 8) are generally described as being thermoplastic when comprised of 16-40% acrylic and/or methacrylic acid, and 30-80% methyl acrylate, and which may also contain alkyl esters of acrylic and/or methacrylic acid (see, column 2, lines 54-61, and claim 1).

The copolymers of the '189 patent are anionic polymers. The compositions described in the '189 patent have characteristics which make them thermoplastic, and require particular conditions and excipients as defined therein in order to be molded, see Column 2, lines 20 to 36. However, this description and the claims of the Lehman I patent do **not** describe the polymeric component used herein, known as Eudragit 4135F. This particular copolymer is described in Column 6, as emulsion polymer E2. The E2 polymer contains 10% methacrylic acid, **not** the 16-40% w/w which is stated as being within the compositions having thermoplastic moldable characteristics. In Lehman, the E2 copolymer is also **not** admixed with the additional agents as stated on Column 3, lines 62 to 67, and Column 4, lines 1 and 2 therein.

Applicants specification, page 24, lines 1 to 3 states that the polymers described in the '189 patent have increased viscosity's relative to the blended compositions as used herein. There is no motivation, or teachings in the Lehman I patent to change the viscosity of the compositions in the manner as claimed herein to achieve Applicants invention. Viscosity changes are necessary in order to readily extrude and injection mold the components. See Figure 15 of the instant application (reproduced below) which compares the virgin 4135F polymer with a representative composition of the instant invention, Example 1.



The Examiner states that Petereit teaches use of the:

> "same lubricant, such as stearyl alcohol, for the same purpose namely as a mold releasing agent (paragraphs 0041-0044). Further, the use of lubricant as a mold releaseing agent in the claimed amount is known in the art. See for example the teaching of Lehmann at column 3, lines 65-67l and example 1. Lehmann teaches the use 6% of the mold releasing agent, based on the weight of the polymer" (see page 4, Office Action).

Lehmann teaches use of a mold-release agent which is disclosed as glycerol monostearate and di-stearate, mixtures of these two and stearic acid, and metal salts thereof. Lehmann does not teach nor suggest use of stearyl alcohol. Example 1 of Lehmann does disclose 6% by wt of glycerol monostearate.

Petereit discloses 0.1 to 3% by wt of a release agent in paragraph 0041:

> **[0041]** The mixture comprises from 0.1 to 3% by weight, preferably from 0.2 to 1% by weight, of a release agent, based on the (meth)acrylate copolymer.

Petereit discloses Paragraph 0043-44 describe suitable mold release agents:

[0043] Examples of release agents (mould-release agents) are:

[0044] esters of fatty acids or fatty amides, aliphatic long-chain carboxylic acids, fatty alcohols and esters of these, montan waxes, paraffin waxes, and metal soaps, and particular mention should be made of glycerol monostearate, stearyl alcohol, glycerol behenate, cetyl alcohol, palmitic acid, canauba wax, beeswax, etc.

The Examiner states that "it would have been obvious to one of ordinary skill in the art to modify the molding composition of Petereit using lubricant in the claimed amount in view of the teaching of Lehmann".

Applicant's claim 1 has a "lubricant present in an amount of 5 to about 30% w/w". Claim 7, dependent upon claim 1 has "the lubricant is present in an amount of about 10 to 25 % w/w". Claim 9 is directed to stearyl alcohol, and claim 10 is wherein "the stearyl alcohol is present from about 10 to about 15% w/w".

The Examiner's argument does not make sense however. Lehman discloses glycerol monostearate. Petereit includes glycerol monostearate in their list of mold-release agents. In fact, Example 2 of Petereit uses glycerol monostearate. Petereit is an improvement by the same manufacturer as Lehmann. Petereit specifically choose to reduce the amount of mold release agent needed in the formulation used in the process therein. There would be no motivation to direct the skilled artisan to then increase the amount of mold release agent in the Petereit formulation. There is no suggestion or teaching in Petereit or Lehmann to use 10-25% w/w of a mold release agent (as required in claim 7). There is no teaching or suggestion to specifically use stearyl alcohol in amounts of about 10 to about 15% w/w as required by claim 9.

Consequently all of the limitations of Claim 1, and those dependent thereon that are not present in the '042 publication are not achieved by the teachings of Lehman I patent.

The mere fact that references can be combined or modified is not sufficient to establish *prima facie* obviousness. MPEP § 2143.01 at 2100-131. There must be something in the prior art to suggest the desirability of the combination. *Id.; see also, In re Mills,* 916 F.2d 680, 16 U.S.P.Q. 2d 1430 (Fed. Cir. 1990).

There is nothing in Lehman I to explain the incorporation of particular substituents, such as a combination of two dissolution modifying excipients (Claim 1) or a combination of a swellable solid and lactose, or super disintegrant (Claim 16), or a combination of two dissolution modifying excipients and a surfactant (Claim 1 and 18), etc., with similar claims for the linker subunit.

Indeed, the Lehman et al. reference would teach the skilled artisan that Applicants additional excipients and additives are not needed as their thermoplastic compositions are deemed suitable for molding based solely upon the addition of glycerol monostearate as a mold release agent. This would suggest that the skilled person that would not be motivated to make any substitution or additions whatsoever to the compositions of Lehman. The skilled artisan

This also does not address the inclusion of a combination of dissolution modifying excipients, the specific w/w% amounts of these excipients and of the lubricants and surfactants as claimed by Applicants. As noted above, the Examiner has also not provided any basis for an article of manufacture which is the linker subunit. Although the linker composition is the same as that of the capsule shell wall, it is a linker subunit which is being claimed having that composition, not the composition itself. No cited references teach or describe this unit, having these particular characteristics

It should be noted that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention **where there is some teaching, suggestion or motivation to do so** found either in the references or in the knowledge generally available to one of ordinary skill in the art. The test for obviousness is not whether the features of the secondary references may be bodily incorporated into the structure of the primary reference; nor is it that the claimed invention must be expressly suggested in any one or all of the references. Rather, the test is **what the combined teachings** of the references would have suggested to those of ordinary skill in the art.

Even with the combined teachings of the references discussed above, nothing therein would teach, suggest or motivate one of ordinary skill in the art to combine these teachings to obtain the presently claimed molded capsule shell or dosage unit compositions.

Therefore, the USPTO has failed to establish a *prima facie* case of obviousness for the claims as presented herein.

II. Rejection of Claims 3-6, 18 and 75-80 under 35 USC §103(a) over Petereit in view of Bolles (US 3,779,942) and Zentner (US 4,795,644)

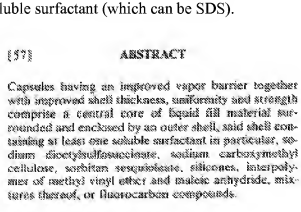
Claims 3-6, 18 and 75-80 are rejected under 35 USC §103(a) as being unpatentable over Petereit (US Pub. No. 2002/0160042) in view of Bolles (US 3,779,942, herein after '942) and Zentner (US 4,795,644, herein after '644). Applicants respectfully traverse this rejection.

For all the reasons described previously in the first §103(a) rejection which is incorporated herein there is no teaching, suggestion, motivation or reason provided in Petereit for making capsule shell and linker compositions that are substantially pH independent, and have the required limitations as shown in Claim 1 herein.

The Examiner cites the '942 Bolles reference for teaching a capsule shell composition comprising well known polymers such as:

> "hydroxypropylcellulose, and a surfactant such as sodium dioctyl sulfosuccinate in an amount of from about 0.001-10% (abstract; and column 2, lines 20-59)". (See Office Action, page 5, 4th ¶).

There is no mention of HPC in the abstract. The abstract (shown below), discusses a liquid fill material surrounded and enclosed by an outer shell, the outer shell containing at least one soluble surfactant (which can be SDS).



[57] **ABSTRACT**

Capsules having an improved vapor barrier together with improved shell thickness, uniformity and strength comprise a central core of liquid fill material surrounded and enclosed by an outer shell, said shell containing at least one soluble surfactant in particular, sodium dioctylsulfosuccinate, sodium carboxymethyl cellulose, sorbitan sesquioleate, silicones, interpolymer of methyl vinyl ether and maleic anhydride, mixtures thereof, or fluorocarbon compounds.

Column 2 of the '942 patent discusses compatible surfactants for use in the soft fill capsule. The polymer hydroxypropylcellulose is mentioned on column 1, lines 67 onto column 2,

lines 1-2. Example 18 of the '942 patent appears to use hydroxypropylmethylcellulose and Example 20 appears to use hydroxypropylcellulose C to make the soft capsule shell.

The '942 patent references US patent 3,423,489 ('489) as the apparatus and method for the encapsulation technology used in the improvement disclosed therein. The process of the '489 patent produces not an extruded and injection molded subunit as required by the claims herein, but a liquid filled encapsulated soft capsule capsule.

The temperature and pressures needed to extrude and injection mold the shells and linker subunits herein is not the same as that of the encapsulation process. The general process used in the '489 patent is shown below, taken from Column 2, lines 18-61:

This invention makes possible the formation of capsules by physical means at extremely high production rates, in the order of 30,000 to 120,000 capsules per minute per nozzle, and by virtue of its ability to encapsulate aqueous liquids makes possible for the first time the economically practical encapsulation of water soluble chemical components for subsequent use in chemically reactive systems. The invention further makes possible the production of well-formed capsules having excellent sphericity, uniform wall thicknesses, and leakproofness. In some embodiments, unlike previously known processes, the process is independent of the surface tensions of the liquids, i.e., it is possible to encapsulate low surface tension liquids within high surface tension liquids.

Briefly summarized, the present invention involves forming a concentric biliquid column having an inner core of liquid to be encapsulated and an outer tube of hardenable liquid encapsulating material which is caused to travel as a stream in a trajectory path for a time sufficient to allow the column to constrict due to natural forces, i.e. cohesive forces, surface tension and the like, first into a "string of capsules" and then ultimately into individual droplets or capsules in which the encapsulating material completely encloses the encapsulated liquid. The encapsulating material is congealed sufficiently upon separation of the stream into individual capsules to withstand impact upon falling. If desired the process conditions can be controlled to produce connected strings of capsules by congealing the encapsulating material sufficiently to maintain the connecting strands intact, thus preventing separation of the stream into individual capsules. It is much preferred to direct the biliquid column or stream to travel through a gaseous medium, such as air in a state or free fall in a trajectory path having horizontal components, rather than into a liquid medium.

A preferred method of forming a biliquid column is by forcing a jet of fill liquid through a body of liquid encapsulating material, the jet being directed to cause the resulting biliquid column to follow the desired trajectory. The column is apparently formed by frictional forces between the fast moving jet of fill liquid and the encapsulating liquid which entrains the fill liquid stream to drag along with it a concentric shell of the encapsulating liquid, which shell is rapidly accelerated to a velocity equal to that of the fill liquid so due to encapsulant as above

The soft liquid fill capsule obtained by the process of the '489 and the addition of the surfactants in the '942 patent do not teach nor suggest a pH independent copolymer blend of methyl acrylate, methyl methacrylate and methacrylic acid polymers which are pH independent, and release the contents of their rigid capsule shell within particular parameters.

In contrast to the '942 soft capsule, the shell of the claimed invention is required to have a wall thickness in the range of about 0.3 – 0.8 mm (Claim 112). It is unclear how the Examiner would achieve this limitation using the technology of the '942 patent. Additionally, the article claimed herein is a subunit. The subunits are meant to be assembled together to a multi-compartment unit, including a shell and a linker and optionally additional shells. The '942 patent does not produce a 'subunit'. It does not produce a unit which can be filled with other than a liquid.

As distinguished from the claimed invention, the '942 patent produces a completed unit dosage form, whereas the instant claims merely produce shells and subunits which can be filled and clipped/welded with other filled subunits having differing actives. The '942 will only be liquid filled with one active. The '942 capsule is not directed towards having multiple subunits with differing release rates. The'942 capsule is not going to be able to achieve multiple subunits with differing release rates and different actives (if desired).

The Bolles reference would not teach or direct the skilled artisan to add a polymer such as 4135F to the encapsulation formulation, nor be motivated to alter the Petereit thermoplastic compositions suitable for molding and achieve the molded articles as claimed herein. The additional excipients and additives which are missing from the Petereit reference, are not satisfied by the teachings of Bolles.

Bolles also does not address the inclusion of a combination of dissolution modifying excipients, the specific w/w% amounts of these excipients and of the lubricants and surfactants as claimed by Applicants. It solely addresses surfactants within a completely different system.

The Zentner reference is cited by the Examiner for is inclusion of a particular surfactant (see Office Action, page 5 last line). The Zentner device is directed to a rather complex drug delivery device which uses charged insoluble resins bearing electrostatic charges identical to that of the intended drug to be used in the device. The drug needs to be a water-soluble diffusible ionized drug. There is no such requirement for this in the instant invention.

Zentner delivers a drug as a controlled rate of release. The goal of Zentner is to deliver to the GI tract a drug at a substantially constant rate, regardless of the pH of the GI tract (See column 2, lines 63-69). The device is also meant to maintain its physical and chemical integrity throughout the release period (column 3, lines 12-14). This is clearly not what the instant invention is intended to do.

In the present invention:

1) the capsule shell and/or linker is meant to break apart at a particular time, and release the contents of the shell/linker to the GI tract at that time, all at once, not over a period of time to provide a controlled constant rate of release;

2) the 4135F polymeric formulations provide for a capsule shell that has a more delayed, or prolonged time period to release the capsule contents into the GI tract; than a gelatin capsule which is of the immediate release;

3) when a multicomponent dosage form of the present invention, is assembled it is possible to have a shell subunit that disperses the contents as an immediate release, and be linked to a second, or third, etc. shell subunit that disperses the contents as pulsitile releases, much later down the GI tract; and

4) prior to the disclosure by Applicants it was not believed possible to prepare a pH-independent **capsule shell or linker itself** using the copolymers as recited in the presently amended claims.

Neither the Petereit reference alone or taken with Bolles or Zentner teaches the skilled artisan how to achieve these individual components, alone or as a multicompartment dosage form having the characteristics as described herein.

The reasons for inclusions of lubricants or surfactants within the Bolles or Zentner disclosure does not provide any meaning for inclusion within the instant formulation. Neither of these references have the same issues or problems encountered by Applicants in their development. Neither Bolles nor Zentner teach extruded and injection molded components.

Simply because Zentner includes a surfactant into the disclosed device does not direct the skilled artisan to look at this device and extrapolate it use therein for a completely different activity.

There is no teaching, suggestion, motivation or reason for one of ordinary skill in the art to use the teachings of Petereit alone or with Bolles and Zentner to result in the substantially pH independent composition and articles of manufacture as claimed in the present invention. Bolles and Zentner do not make up for the deficiencies of Petereit with respect to changing the pH dependency of the compositions described in those references, and in fact further exemplifies the unexpectedness of the presently claimed invention.

Therefore, the claimed invention is not prima facie obvious, and withdrawal of the rejection of these claims under 35 USC §103(a) is respectfully requested.

III. Rejection of Claims 1-33, 35, 38-40, 71-97, 112-132 and 134 under 35 USC §103(a) over Petereit, in view of Lehmann I, Hatano (US 6,309,666) and Klug et al. (US 3,314809).

Claims 1-33, 35, 38-40, 71-97, 112-132 and 134 are rejected as being unpatentable under 35 USC §103(a) over Petereit (US2002/0160042), in view of Lehmann (US 5,705,189, also referred to therein as Lehman I), Hatano (US 6,309,666) and Klug et al. (US 3,314809, hereinafter '809). Applicants respectfully traverse this rejection.

As Petereit, and Lehman I are discussed supra, please see the above comments. Hatano has also previously been discussed in Applicants prior responses which are incorporated by reference herein.

In summary, Hatano does not disclose a molding process for making capsule shell/linker components, nor the molded articles which are capsule shell and/or linker components. Hatano is interested in providing a modified dosage form which uses pre-existing capsule shells and coats these shells to provide for particular release features.

The Hatano et al. patent discloses a pulse release dosage form having the following characteristics:

1. An enteric layer (acrylic copolymer) that dissolves when the unit enters the small intestine and is exposed to pH>5.5;
2. An inner layer of the Eudragit E100 polymer that swells and hydrates, but does not dissolve;

3. Fluid enters the capsule body (dissolving the gelatin or HPMC capsule shell wall) at a rate determined by the thickness of the E100 coating and begins to dissolve the acidic capsule contents, and

4. Dissolution of the E100 layer is controlled by the amount and/or type of acid contained within the capsule fill, and the thickness of the E100 coating.

The film-coating usage disclosed in Hatano this form a multi-layer construct of film coats on top of a capsule shell wall, wherein the hard capsule shell has both an enteric coating and an inner layer coating applied on top of the capsule shell wall. It is the combination of coatings on the shell that provide for the delayed release characteristics of the final dosage form as shown in Hatano. The film-coating composition controls the release of the contents of the capsule shell which it surrounds. In contrast it is the composition of the shell itself (when injection molded into the capsule shell) when combined with other capsule shells and/or linker subunits of the same or differing compositions that control the release of the release of the contents of the capsule shell. A skilled artisan would not look to the Hatano to achieve a formulation that is pH independent, nor a formulation that can be extruded and injection molded into an article of manufacture.

Klug '809 patent appears to be cited by the Examiner for a teaching of a capsule shell that comprises HPC. (See Office Action, page 7, 2nd ¶). The Klug patent describes a process for making thermoplastic articles with an HPC polymer. The HPC used in the Klug process is the primary polymer and requires a particular degree of substitution, etc. for use therein. While Klug provides for additional excipients which can be added, they are limited to "anti-oxidants, fillers, pigment and the like" without any specific embodiments being listed. (See Column 5, lines 12-16).

As noted supra, Petereit provides for incorporation of another polymer into the blend (see paragraph 0080) but does not provide for combinations of these polymers in the blend. Petereit is also unclear as to whether HPMC or HPC was meant to be included in the long list of suitable and additional polymers which might be added to the formulation.

As noted, Klug is cited by the Examiner to teach that the skilled artisan would be motivated to select HPC as the "other" polymer to be added to the capsule shell composition of Petereit. Given the ambiguity displayed in Petereit this is an improper conclusion and is improperly using hindsight rejection in view of Applicants disclosure. However, even if this

were true, why would the skilled artisan necessarily pick and choose a swellable solid which is HPC or HPMC from the long list of polymers cited in Petereit?

More specifically, Petereit taken with any of these references does not teach a combination of excipients as required in Claim 1. Lehman I does not teach nor suggest all the limitations present in claim 1. The secondary references of Hatano do not provide the missing excipients, nor does Klug.

Consequently, none of the references alone or in combination, provides any teaching, suggestion, or motivation to one of ordinary skill in the art to combine these references to and obtain a pH independent capsule shell or linker subunit having the claimed composition herein. Therefore, reconsideration, and withdrawal of the rejection of these claims under 35 USC §103(a) is respectfully requested.

In response to Applicants prior arguments, the Examiner comments "that nowhere in the Petereit reference is there a teaching of pH-dependency disclosed". The argument appears to be made that Petereit teaches the use of the same copolymer and in the same amount. "Where the claimed and prior art products are identical or substantially identical in structure or composition, a prima facie case of either anticipation or obviousness has been established". (See Office Action, page 8, 1rst full ¶).

Applicants contest the Examiner's view that the Petereit reference teaches "identical or substantially identical in structure or composition" to that claimed herein. As has been pointed out above, the limitations of Claim 1 have not been achieved by Petereit alone or in combination with the various cited references. The naked or virgin polymer does not dissolve in a pH independent manner. The instant application provides clear data that the compositions, when tested as a capsule shell with drug. in a USP II or III apparatus in suitable media, such as SIF do not display pH dependency but are independent of pH in their release of the contents. This limitation in Claim 1 is not the only difference between Applicants and the rejections under 35 USC §103(a) herein.

The appropriate test is **what the combined teachings** of the references would have suggested to those of ordinary skill in the art. Even with the combined teachings of the references discussed above, nothing therein would teach, suggest or motivate one of

ordinary skill in the art to combine these teachings to obtain the presently claimed molded capsule shell or dosage unit compositions.

Therefore, the USPTO has failed to establish a *prima facie* case of obviousness for the claims as presented herein.

Applicants respectfully request withdrawal of each of the above identified rejections to the claims under 35 USC §103(a).

CONCLUSION

Reconsideration and withdrawal of the rejections based on 35 USC §112 and §103, and the prompt issuance of a Notice of Allowance, is respectfully requested. Should the Examiner have any questions or wish to discuss any aspect of this application, the Examiner is encouraged to call the undersigned attorney at the number below. If the Examiner does not find the claims allowable, Applicants respectfully request an interview with the Examiner at the earliest opportunity.

It is not believed that this paper should cause any additional fees or charges to be required, other than expressly provided for already. However, if this is not the case the Commissioner is hereby authorized to charge Deposit account 19-2570 accordingly.

Respectfully submitted,

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Preliminary specifications, test methods and processing characteristics for Präparat 4135 F (Preparation 4135 F)

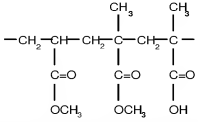
Preliminary specifications

1 Commercial form

Solid substance obtained from EUDRAGIT® FS 30 D by stress coagulation and extrusion, the product contains small amounts of Sodium Laurylsulfate Ph. Eur. / NF. and Polysorbate 80 Ph. Eur. / NF.

2 Chemical structure

Präparat 4135 F is a copolymer of methyl acrylate, methyl methacrylate and methacrylic acid.



The ratio of the free carboxyl groups to the ester groups is approx. 1:10.
The average molecular weight is approx. 220,000.

3 Characters

Description

Colourless to yellow tinged granules with a faint characteristic odour

Solubility

1 g of Präparat 4135 F dissolves in 7 g aqueous acetone (H_2O 3% w/w) to give a clear solution or in 7 g 1 N sodium hydroxide solution to give a slightly cloudy solution.
The solid substance is practically insoluble in petroleum ether.

4 Tests

Dry substance (DS)
Not less than 97 %.
According to Ph.Eur. "Loss on drying", method d, approx. 1 g of the granules is dried for 3 hours at 110°C.

Assay
9.2 – 12.3 % methacrylic acid units on dry substance (DS)

Acid value: 60 - 80 mg KOH per g of dry substance

The assay is performed according to Ph. Eur. "Potentiometric titration" or USP <541>.
Approx. 2.0 g of Präparat 4135 F are dissolved in 90 ml isopropyl alcohol and 10 ml water.
Titration is performed with 0.5 N sodium hydroxide (NaOH).
A blank value is determined under the same conditions.
1 ml 0.5 N NaOH corresponds to 43.045 mg methacrylic acid units.

$$\text{Methacrylic acid units (\%) on DS} = \frac{\text{ml 0.5 N NaOH} \cdot 430.45}{\text{sample weight (g)} \cdot \text{DS (\%)}}$$

The acid value (AV) states how many mg KOH are required to neutralize the acid groups contained in 1 g dry substance.

AV (mg KOH / g DS) = methacrylic acid units (%) · 6.517

5 Purity

Sulphated ash / Residue on ignition
Max. 0.2 % according to Ph. Eur. 2.4.14 or USP <281>.
1 g Präparat 4135 F is used for the test

Heavy metals
Max. 20 ppm according to Ph. Eur. 2.4.8 method C or USP <231> method II.
1 g Präparat 4135 F is used for the test.

Monomers
Max. 500 ppm, determined by means of liquid chromatography according to Ph. Eur. 2.2.29 or USP <621>.

Sample solution:
Dissolve 1.00 g of Präparat 4135 F in acetone p.a. and dilute to 50.0 ml.
Add 10.0 ml of the solution drop wise to 40 ml of a 70 % solution of methanol for chromatography in water. Centrifuge for 5 min at 6000 rpm and use the supernatant solution as the test solution.

Reference solutions:
Pipette 10.0 mg of methyl acrylate to 5 ml of iso-butanol and dilute to 50.0 ml with acetone p.a. Dilute 1.0 ml of the solution to 100.0 ml with acetone p.a. Take 10.0 ml of this solution and mix with 40 ml of a 70% solution of methanol for chromatography in water. Pipette 10.0 mg of methacrylic acid and 10.0 mg of methyl methacrylate to 5 ml of iso-butanol and dilute to 50.0 ml with acetone p.a. Dilute 1.0 ml of the solution to 100.0 ml with acetone p.a. Take 10.0 ml of this solution and mix with 40 ml of a 70 % solution of methanol for chromatography in water.

Procedure: The chromatographic procedure may be carried out using:
- a column 120 mm long and 4.6 mm in internal diameter packed with octadecylsilyl silica gel for chromatography R (7 µm) Ph. Eur. (USP: L1),
- as mobile phase at a flow rate of 2 ml per minute a mixture of 20 volumes of methanol R and 80 volumes of phosphoric acid pH 3.8,
- as detector a spectrophotometer set at 200 nm.

Inject separately equal volumes (about 20 µl) of each solution.

Calculate the content of monomers from the height of the peaks in the chromatograms obtained with the sample solution and the reference solutions, from the content of monomers in the reference solutions and from the sample weight.

Microbial count
Max. 1,000 CFU / g; Salmonella not detectable in 10 g, E. coli, S. aureus, Ps. aeruginosa not detectable in 1 g. The test is performed according to Ph. Eur. 2.6.12 and 2.6.13.

6 Identity testing

Proof of identity is furnished by IR spectroscopy on a dry film of Präparat 4135 F approx. 15 µm thick.

To obtain the film, some drops of an approx.10 - 15 % solution of Präparat 4135 F in acetone is placed on a crystal disc of KBr and dried in vacuum for about 2 hours at 70 °C.

The location and intensity of the bands correspond to Figure 1.
The figure shows the characteristic band of the C = O vibrations of the esterified carboxyl groups at 1732 cm^{-1}, which overlaps the band of the C = O vibrations of the carboxylic acid groups at 1705 cm^{-1}. Further ester vibrations are detected at 1166, 1196, 1235 and 1263 cm^{-1}. The wide absorption range of associated OH Groups between 2500 and 3500 cm^{-1} is superimposed by CH_x vibrations at 2900 – 3000 cm^{-1}. Further CH_x vibrations can be discerned at 1386, 1439 and 1447 cm^{-1}.

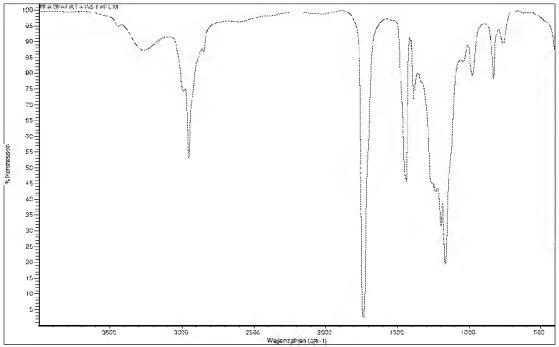


Figure 1: IR spectrum of Präparat 4135 F

7. Storage and handling:

Protect from warm temperature (USP, General Notices)
Protect from moisture.

8. Stability:

Storage stability data are available upon request.

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